Provisional Rejection of Claims 1-15, 26 Under the Judicially-Created Doctrine of Obviousness-Type Double Patenting

Claims 1-15 and 26 stand rejected under the judicially-created doctrine of obviousness-type double patenting. Claims 1-15, and 26 are said to be unpatentable over the claims of co-pending Application No. 09/406,568 (now U.S. Patent No. 6,468,967). Consistent with current Patent Office practice, Applicants elect to defer any action (such as the filing of a terminal disclaimer) until such time as the Examiner has indicated that there is allowable subject matter.

The Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-4, 11, 13-15, and 26 stand rejected under 35 U.S.C. § 112, first paragraph. The Office Action states that the specification, while enabling for methods of administering daptomycin such that it does not cause muscle toxicity, does not reasonably provide enablement for methods of administering daptomycin derivatives, A54145, A54145 derivatives or other lipopeptide antibiotics in such a manner that they do not cause muscle toxicity. The Office Action states that it is well known in the art that even structurally similar antibiotics can have different modes and ranges of toxicity (Remington's pp. 1176-1213). Finally the Office Action asserts that "without working examples a skilled artisan would be required to perform undue experimentation in order to determine first whether the same also cause muscle toxicity and second the suitable doses and intervals which would not exhibit muscle toxicity for which would not exhibit muscle toxicity for the daptomycin derivatives, A54145, A54145 derivatives or other lipopeptide antibiotics." Applicants respectfully traverse.

Applicants respectfully submit that administration of daptomycin is a preferred embodiment of the present invention and the present invention, as exemplified for daptomycin, is applicable to other lipopeptide antibiotics, as described in the specification by their structural characteristics. See, e.g., page 11 lines 4-6. Thus,

Applicants respectfully submit that the species daptomycin is representative of the genus lipopeptide antibiotics. Therefore, methods of administering daptomycin in a manner that minimizes muscle toxicity are equally applicable to methods of administering daptomycin derivatives, A54145, A54145 derivatives or other lipopeptide antibiotics in such a manner that minimizes muscle toxicity. Moreover, to the extent that any experimentation would be necessary, such experimentation would not be an undue amount because the skilled artisan can simply follow the clear teachings of Applicants' "working example." The clear guidance in Applicants' specification, in combination with the commensurate dose and interval limitations in the pending claims, compel the conclusion that the pending claims are sufficiently enabled by the specification.

Accordingly, Applicants respectfully submit that pending claims 1, 3-4, 11, 13-15, and 26 are sufficiently enabled by the specification, and request reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 6-15 and 26 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to set forth the subject mater which applicants regard as their invention. The Office Action states that the claims fail to recite an essential element of the invention, which is that the antibiotic does not cause muscle toxicity. Applicants respectfully traverse.

Applicants respectfully submit that 35 U.S.C. § 112, second paragraph, does not require recitation of "essential" elements. Nevertheless, to expedite prosecution, Applicants have amended, without prejudice, the pending claims to recite administration of a lipopeptide antibiotic at a dosage interval that minimizes skeletal muscle toxicity, thereby obviating this rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

The Rejections Under 35 U.S.C. §§ 102 and 103

Claims 1-5 and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Pryka et al., DICP The Annals of Pharmacotherapy 24:255-56, 1990 (hereafter "Pryka"). The Office Action states that Pryka expressly discloses a method of administering daptomycin at a dose of 2 mg/kg every 24 hours falling within the scope of Applicants' claims. The Office Action further states that the claimed invention is rendered obvious because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. Applicants respectfully traverse.

Applicants have amended claim 1 to recite a method of administering a lipopeptide antibiotic to a human patient in need thereof at a dose of at least 3 mg/kg at a dosage interval of once every 24 hours to once every 48 hours. Thus, Pryka does not anticipate the claimed methods because, at most, Pryka discloses treating a human patient with 2 mg/kg daptomycin every 24 hours for five days. See p. 255, right column. Furthermore, the claims as amended do not use the same ingredients/components as Pryka because the dose of lipopeptide antibiotic is different from that of Pryka. Pryka also does not render obvious the claimed methods because Pryka does not teach or suggest repeatedly administering a lipopeptide antibiotic at a dose other than 2 mg/kg at an interval of at least 24 hours.

Claims 1-10, and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, rejected under 35 U.S.C. § 103(a) as obvious over Kennedy et al., Antimicrobial Agents and Chemotherapy 33:1522-25, 1989 (hereafter "Kennedy"). The Office Action asserts that Kennedy discloses a method of administering daptomycin at a dose of 10 mg/kg as a single daily dose, which falls within the scope of Applicants' claims. The Office Action asserts that, alternatively, the claimed invention is rendered obvious in view of Kennedy because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. Applicants respectfully traverse.

As discussed above, applicants have amended the pending claims to recite a method of repeatedly administering a lipopeptide antibiotic to a human patient in need thereof at a dose of at least 3 mg/kg at a dosage interval of once every 24 hours to once every 48 hours. In contrast, Kennedy discloses a method of preventing experimental aortic valve endocarditis in rabbits by administering a single dose of 10 mg/kg daptomycin. See page 1522, right column. The prevention method disclosed by Kennedy cannot anticipate the claimed invention because it discloses administering only a single dose to a rabbit, not a repeated dose to a human patient.

Kennedy also discloses a method of treating experimental aortic valve endocarditis by administering 10 mg/kg daptomycin to a rabbit every 24 hours for two to four days. See page 1522, right column. The treatment method disclosed by Kennedy does not anticipate the claimed invention because it does not disclose repeated lipopeptide antibiotic administration to a human patient. In addition, Kennedy does not teach or suggest repeatedly administering a lipopeptide antibiotic at a concentration of at least 3 mg/kg at a frequency of once every 24 hours to once every 48 hours to a human patient. Further, one of ordinary skill in the art would have recognized that a dose of 10 mg/kg every 24 hours in a rabbit is equivalent to a dose of 0.84 mg/kg every 24 hours in a human. This is more than three times lower than the lowest dose claimed by applicants. Thus, one of ordinary skill in the art would have recognized that these data disclosed by Kennedy doe not teach or suggest a higher dose in human patients, as recited in the pending claims. For these reasons alone, Kennedy does not render the pending claims obvious.

Further, one of ordinary skill in the art would not have been motivated by Kennedy to administer more than three times the equivalent human dose disclosed by Kennedy because Kennedy only addresses the efficacy of daptomycin and does not address daptomycin's toxicity. Because clinical trials of daptomycin were suspended because of its adverse effects at high doses, the toxicity of daptomycin was a significant problem in the art that Kennedy does not even address, let alone teach or suggest a

solution to the problem. One of ordinary skill would have considered that daptomycin's toxicity would preclude administering daptomycin to a human patient at a dose more than three times higher than that taught by Kennedy. Thus, one of ordinary skill in the art would not be motivated by Kennedy to administer a dose of greater than three times the equivalent dose to humans as is claimed by applicants because one of ordinary skill in the art would expect that a higher dose would cause muscle toxicity.

Kennedy also suggests that administration of more than 10 mg/kg and at a greater frequency than a single daily dose may be needed to treat endocarditis, which teaches away from the instant invention. See p.1524, right column. Following Kennedy's suggestion of administration of a higher dose more frequently than once a day would have led one skilled in the art to a dosage protocol that would have been likely to cause skeletal muscle toxicity as, it is known that administration of 4 mg/kg every 12 hours leads to skeletal muscle toxicity. Thus, for all of the above reasons, the pending claims are neither anticipated by nor obvious over Kennedy. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections based on Kennedy.

Claims 1-5, 11-15 and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, rejected under 35 U.S.C. § 103(a) as obvious over Van der Auwera, Antimicrobial Agents and Chemotherapy 33:1783-90, 1989 (hereafter "Van der Auwera"). The Office Action states that Van der Auwera discloses a method of administering daptomycin in a single dose of 1 or 2 mg/kg combined with amikacin falling within the scope of applicants' claims. The Office Action further states that the claimed invention is rendered obvious because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. Applicants respectfully traverse.

As discussed above, the pending claims recite a method of repeatedly administering a lipopeptide antibiotic to a human patient in need thereof at a dose of at least 3 mg/kg at a dosage interval of once every 24 hours to once every 48 hours. Claims 11-15 recite a method of repeatedly administering a lipopeptide antibiotic to a human

patient in need thereof at a dose of at least 3 mg/kg at an interval of once every 24 hours to once every 48 hours in combination with another antibiotic. Claim 26 recites a method of repeatedly administering lipopeptide antibiotic/daptomycin to a human patient in need thereof at a dose of at least 3 mg/kg at an interval of once every 24 hours to once every 48 hours, wherein the administration is oral, intravenous or subcutaneous. At most, Van der Auwera discloses administration of a single dose of 1 or 2 mg/kg daptomycin or a single dose of daptomycin in combination with 500 mg amikacin to healthy human volunteers. See p. 1783, right column. Van der Auwera does not disclose repeated administration of at least 3 mg/kg of a lipopeptide antibiotic in combination with another antibiotic to a human patient in need thereof, and thus does not anticipate the pending claims.

The claims as amended also do not use the same ingredients/ components as Van der Auwera because the dose of lipopeptide antibiotic recited in the pending claims is different from that of Van der Auwera, which only recites administering 1 or 2 mg/kg daptomycin. Further, Van der Auwera states that "the results reported here preclude the administration of daptomycin as a single daily dose (1 and 2 mg/kg) and support administration twice a day." See p. 1789, right column (emphasis added). Thus, Van der Auwera teaches away from Applicant's claimed administration of a lipopeptide antibiotic as a single daily dose.

In addition, Van der Auwera, like Kennedy, only addresses the efficacy of daptomycin and does not consider daptomycin's safety. As discussed above, daptomycin was known to have adverse effects at high doses. Thus, one of ordinary skill in the art would have expected that daptomycin's toxicity would prevent repeated administration of daptomycin to a human patient at a dose higher than 1 or 2 mg/kg, with or without other antibiotics. Further, one of ordinary skill in the art would have recognized that Van der Auwera's administration of a single dose of daptomycin or daptomycin in combination with another antibiotic, is not predictive of administration of repeated doses with respect to, *inter alia*, toxicity and daptomycin accumulation. Thus, it would not have been obvious to use once daily dosing of a lipopeptide antibiotic because one having ordinary

skill in the art would expect that repeated administration of a lipopeptide, such as daptomycin, at a higher dose than that disclosed by Van der Auwera would cause muscle toxicity.

The Office Action states that claims 1-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the acknowledged prior art in view of Pryka, Kennedy and Van der Auwera.*

The Office Action states that applicants acknowledge that it was known in the art that low doses of daptomycin did not cause muscle toxicity but that higher doses may be necessary to treat resistant strains of bacteria. The Office Action also states that it was known in the art that 4 mg/kg doses of daptomycin at 12 hour intervals was toxic to muscle but that single doses (0.5 to 6 mg/kg) or doses of 1 to 2 mg/kg of daptomycin every 24 hours were well tolerated.

The Office Action contends that Pryka, Kennedy and Van der Auwera teach that higher doses of daptomycin given in a single dose or at least every 24 hours are effective in treating infections and are well tolerated. The Office Action further asserts that Van der Auwera teaches that daptomycin may be combined with other antibiotics.

The Office Action asserts that the difference between the prior art and the claimed invention is that the prior art does not expressly disclose that certain higher doses of daptomycin administered at 24 hour intervals or longer will not be toxic to muscles. The Office Action also asserts that the prior art suggests that higher doses are well tolerated at intervals of 24 hours and that one of ordinary skill in the art would have been motivated to modify the prior art with the expectation that increasing the dosing interval would allow higher doses of the above-mentioned antibiotics while keeping muscle toxicity to a minimum. Finally, the Office Action also states that it would have been within the skill of one skilled in the art to arrive at the various doses and intervals by

* Applicants note that while the May 21, 2002 Office Action refers to claims 1-33, only claims 1-15 and 26 were pending. Therefore Applicants will address this rejection with respect to the claims 1-15 and 26 only.

optimization of the prior art values taking into consideration adverse effects on the patient and effective therapeutic range. The Office Action then concludes that the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references. Applicants traverse.

Applicants will address the present rejection only as it applies to the pending claims. As discussed above, the pending claims recite a method of repeatedly administering a lipopeptide antibiotic to a human patient in need thereof at a dose of at least 3 mg/kg at a dosage interval of once every 24 hours to once every 48 hours.

Applicants respectfully submit that the prior art acknowledged by applicants, in combination with Kennedy, Van der Auwera and Pryka, does not render the pending claims obvious.

First, the prior art discussed in Applicants' specification discloses administration at 1 or 2 mg/kg every 24 hours and administration of a single dose of 0.5 to 6 mg/kg. See the specification at p. 2, lines 24-28. Pryka only teaches administration of 2 mg/kg daptomycin once daily and nowhere suggests administration of higher levels of daptomycin. Thus, Pryka teaches no more than the prior art acknowledged by the applicants and relied upon in the Office Action. As discussed above, Kennedy teaches repeated administration with 10 mg/kg every 24 hours in a rabbit, which is equivalent to a dose of 0.84 mg/kg every 24 hours in a human. Thus, Kennedy teaches no more than the acknowledged prior art. The same is true for Van der Auwera. Van der Auwera only teaches a single administration of 1 or 2 mg/kg of daptomycin with another antibiotic. Thus, Van der Auwera teaches no more regarding administering the claimed doses of lipopeptide antibiotic once daily than the acknowledged prior art. Therefore, none of the prior art, either alone or in combination with Pryka, Kennedy and Van der Auwera, teach or suggest the desirability or provide any motivation for modifying the prior art to arrive at the claimed invention.

Second, the prior art does not suggest that higher doses are well tolerated at intervals of 24 hours because one of ordinary skill in the art would not reasonably expect that a single administration of 0.5 to 6 mg/kg daptomycin would be either predictive or suggestive of repeated administration of a lipopeptide antibiotic at those dosage levels. One of ordinary skill in the art would have known that repeated administration of a drug would result in drug accumulation if subsequent doses are administered before elimination of the previous dose. In the case of daptomycin, which has a half-life of 8.5 hours in humans, a person of ordinary skill in the art would expect that accumulation will occur with once daily dosing. Thus, administration of daptomycin to a human once daily would produce higher daptomycin serum concentrations than a single administration of daptomycin.

It was also well known in the art at the time the invention was made that repeated administration of a drug may have a toxic effect. The toxic effect is often clinically undetectable or even absent when only a single dose of a drug is administered. However, repeated administration will result in an accumulation of these toxic effects, which may then become clinically significant. One of ordinary skill in the art at the time the invention was made would have known that this was the case for daptomycin. Therefore, one of ordinary skill in the art, knowing daptomycin's toxic effects upon repeated dosing, would not have reasonably expected that administration of a single dose of daptomycin would be predictive of repeated administration of daptomycin because of the drug exposure by the patient and the accumulation of toxic effects. Furthermore, as discussed above, given the well-known toxic effects of daptomycin after repeated dosing, one of ordinary skill in the art would not have reasonably expected that administration of 3 mg/kg every 24 hours would avoid adverse skeletal muscle effects.

Pryka, Kennedy and Van der Auwera do not provide any teaching or suggestion of how to design an efficacious dosing protocol that avoids skeletal muscle toxicity because these references did not acknowledge that there was such a problem. Further, the acknowledged prior art relied upon in the Office Action does not provide any

teachings or suggestions of how to design an efficacious dosing protocol that avoids skeletal muscle toxicity. Thus, neither the acknowledged prior art nor Pryka, Kennedy and Van der Auwera provide any teaching or suggestion for overcoming toxicity. Given this lack of guidance, there is no motivation in Pryka, Kennedy and Van der Auwera to modify the teachings of the prior art to obtain a dosing regimen for lipopeptides that is both safe and efficacious. Moreover, there is no evidence that one of ordinary skill in the art would have had a reasonable expectation of success that increasing the dosing interval would allow higher doses of the above-mentioned antibiotics while keeping muscle toxicity to a minimum.

Third, one of ordinary skill in the art would not have been motivated to modify the prior art in view of Pryka, Kennedy and Van der Auwera because both Kennedy and Van der Auwera teach away from the claimed invention. As discussed above, Kennedy suggests that improved efficacy would be achieved by administration of higher doses and at a greater frequency than a single daily dose. See Kennedy, p. 1524, right column. Administration of a higher dose more frequently than once a day had been shown to cause skeletal muscle toxicity in clinical trials. Van der Auwera concludes that "the results reported here *preclude* the administration of daptomycin as a single daily dose (1 and 2 mg/kg) and support administration twice a day." See p. 1789, right column (emphasis added). Thus, Van der Auwera, like Kennedy, teaches away from administration of lipopeptide as a single daily dose. Further, Pryka neither teaches nor suggests modifying its dosing regimen of 2 mg/kg once every 24 hours, and thus cannot cure the defects of Kennedy and Van der Auwera.

Fourth, the facts of record compel the conclusion that it would not have been obvious to repeatedly administer at least 3 mg/kg of a lipopeptide antibiotic no more often than once every 24 hours. Prior to Applicants' invention, substantial research and financial resources were devoted to developing daptomycin for clinical use, but these efforts failed to solve the problem of skeletal muscle toxicity that occurred with efficacious doses. In addition, a number of pharmaceutical and biotechnology companies

declined the opportunity to license daptomycin because of the skeletal muscle toxicity. None of these pharmaceutical companies considered that it would be simple to overcome the problem of daptomycin's skeletal muscle toxicity when administered at doses high enough to eradicate deep-seated infections. It was not until Applicant's invention that a solution to the toxicity problem was found.

Baltz also demonstrates that the problem of daptomycin's toxicity was not solved in 1997, six years after clinical trials were halted, even though a number of post-clinical studies had been conducted. See Baltz at p. 425-26. Baltz, therefore, is representative of the state of the art at the time that Cubist licensed daptomycin from Lilly and began its work to determine how to administer daptomycin safely and efficaciously. Baltz states that one study suggested that the way to overcome the clinical failures at a dose of 2 mg/kg once daily would be to administer higher daptomycin doses at more frequent dosing intervals in order to maintain adequate blood concentrations of daptomycin. Baltz also states that another study suggested administering daptomycin in combination with another antibiotic twice daily. See *Id.* at pp. 424 and 426. Both of these studies teach away from the instant invention. Further, any study that suggested using a higher daily dose of daptomycin to increase efficacy against bacteremia and endocarditis were either done *in vitro* or in experimental animals without any tests for skeletal muscle toxicity. See Baltz, pp. 425-26. Baltz stated that the conclusion of one of these studies was that "the levels of daptomycin needed to treat *E. faecium* endocarditis are probably not safely achievable in humans." See *Id.* at p. 426. Therefore, Baltz compels the conclusion that six years after clinical trials had been suspended because of skeletal muscle toxicity and lack of efficacy for certain types of infection, those of ordinary skill in the art did not know how to solve the problem of daptomycin's toxicity at high doses.

Therefore, for all the reasons presented above, it would not have been obvious to one of ordinary skill in the art to modify the prior art as suggested in the Office

Action. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 1-15 and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the acknowledged prior art in view of Baker et al., United States Patent 5,912,226 (hereafter "the '226 patent"), Woodworth et al., Antimicrobial Agents and Chemotherapy 36: 318-25, 1992 (hereafter "Woodworth"), Watanakunakorn, J. Antimicrobial Chemotherapy 19:445-48, 1987 (hereafter "Watanakunakorn"), Thibault et al., Life Sciences 56: 1877-87, 1995 (hereafter "Thibault") and Leclercq et al., Antimicrobial Agents and Chemotherapy 35: 92-98, 1991 (hereafter "Leclercq"). Applicants respectfully traverse.

The Office Action states that the '226 patent teaches that LY146032 can be used orally, intramuscularly or intravenously, that the effective dose is 0.1 to 100 mg/kg, and that it can be administered as a single daily dose. The Office Action states that Woodworth teaches that administration of single doses of 2, 3, 4 and 6 mg/kg were well-tolerated and that the doses were effective *ex vivo* against bacteria. The Office Action states that Watanakunakorn teaches that LY146032 acts synergistically with gentamicin or tobramycin, that Thibault teaches that daptomycin protects against gentamicin nephrotoxicity, and Leclercq teaches that combinations of antibiotics act synergistically. The Office Actions asserts that the prior art suggests that daptomycin in single daily doses at higher dose rates than 2 mg/kg are well-tolerated and result in no adverse reactions, that combinations of antibiotics act synergistically, and that daptomycin has been shown to prevent gentamicin-induced nephrotoxicity. The Office Action states that it would have been within the skill of one of ordinary skill in the art to administer doses at intervals of 24 hours or higher with the expectation that the administration would not cause muscle toxicity and would be effective in treating various diseases.

Applicants respectfully submit that none of the '226 patent, Woodworth, Watanakunakorn, Thibault, or Leclercq, either alone or in combination, teaches or suggests administration of a lipopeptide antibiotic at a dosage interval that minimizes

skeletal muscle toxicity. First, Woodworth does not teach that "single daily doses at higher dose rates than 2 mg/kg are well tolerated," because Woodworth never administers daptomycin on a daily basis. See, e.g., Woodworth, p. 319, left column. In fact, Woodworth never even suggests repeatedly administering daptomycin once every 24 to once every 48 hours to a patient in need thereof, but rather teaches only administration of daptomycin to healthy volunteers for the purpose of studying daptomycin pharmacokinetics and for determining whether serum from volunteers treated with daptomycin was able to kill bacteria *in vitro*.

Second, none of the '226 patent, Woodworth, Watanakunakorn, Thibault or Leclercq recognizes the problem that skeletal muscle toxicity can be caused by lipopeptide antibiotic administration. The '226 patent discusses only that daptomycin may be administered once daily or multiple times per day. See, e.g., the '226 patent, col. 10, lines 59-61. Watanakunakorn and Leclercq state only that combinations of different antibiotics, including daptomycin, are effective *in vitro* against enterococci, while Thibault states only that daptomycin may protect against gentamicin nephrotoxicity in rats. Because there is no recognition of the potential for skeletal muscle toxicity, none of the references, either alone or in combination, teaches or suggests that dosing once every 24 to once every 48 hours with a lipopeptide antibiotic would minimize skeletal muscle toxicity compared to administration of multiple doses of a lipopeptide antibiotic per day. Further, due to the failure to recognize this problem, there is no motivation in any of the references to combine their teachings with each other to arrive at the claimed invention.

Third, one of ordinary skill in the art would not have had a reasonable expectation of success that this dosing regimen referred to in the '226 patent would minimize skeletal muscle toxicity. The peak concentration of a drug in the bloodstream (C_{max}) is the parameter generally associated with drug toxicity. However, administration of one daptomycin dose per day results in a higher C_{max} than administration of the same total amount of daptomycin divided into many doses over the course of a day. See, e.g., Figure 2 of the instant application. Thus, one of ordinary skill in the art at the time the

invention was made would have expected that administering smaller doses more frequently, which decreases C_{max}, would cause less skeletal muscle toxicity than administering a single larger dose once daily. In fact, one of ordinary skill in the art would have expected that higher doses of daptomycin, such as those that would occur by once daily daptomycin dosing, would cause skeletal muscle toxicity, rather than minimize this toxicity. Thus, one of ordinary skill in the art would not have reasonably expected that once daily daptomycin dosing would minimize skeletal muscle toxicity. None of Woodworth, Thibault, Watanakunakorn or Leclercq, either alone or in combination, remedies this problem because none addresses the issue of skeletal muscle toxicity, much less suggest a solution to the problem. Thus, none of the prior art, either alone or in combination, provides a reasonable expectation of success because none recognizes, addresses or suggests a solution to the problem of skeletal muscle toxicity.

CONCLUSION

For the reasons presented above, Applicants respectfully request reconsideration and prompt allowance of all pending claims.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDED CLAIMS

1. (Amended) A method for administering a lipopeptide antibiotic, comprising the step of administering to a human patient in need thereof a therapeutically effective amount of the lipopeptide antibiotic in a dose of at least 3 mg/kg of the lipopeptide at a dosage interval that [does not result in] minimizes skeletal muscle toxicity, wherein the lipopeptide antibiotic dose is repeatedly administered at a dosage interval of once every 24 hours to once every 48 hours.

3. (Amended) The method according to claim [2] 1, wherein the lipopeptide antibiotic is administered once every 24 hours[to once weekly].

7. (Amended) The method according to claim [6] 1, wherein the dose is 3 to 12 mg/kg.

9. (Amended) The method according to claim [6] 1, wherein the dose is 10 to 25 mg/kg.

11. (Amended) The method according to [either of] claim 1 [or claim 6], wherein an antibiotic other than a lipopeptide antibiotic is co-administered with the lipopeptide antibiotic.

26. (Twice Amended) The method according to [either of claims 1 or 6] claim 1, wherein said administering is via oral, subcutaneous or intravenous administration.